European Society of Surgical Oncology's strategy for clinical research : Paving the way for a culture of research in cancer surgery

European Soc Surgical Oncology

2019-09

European Soc Surgical Oncology 2019 , ' European Society of Surgical Oncology's strategy for clinical research : Paving the way for a culture of research in cancer surgery ' , European Journal of Surgical Oncology , vol. 45 , no. 9 , pp. 1515-1519 . https://doi.org/10.1016/j.ejso.2019.05.004

http://hdl.handle.net/10138/319799
https://doi.org/10.1016/j.ejso.2019.05.004

unspecified
publishedVersion

European Journal of Surgical Oncology 45 (2019) 1515–1519

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

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S. Evrard [a, *], C. van de Velde [b], I. Noordhoek [b], C. Caballero [c], W. Ceelen [d], K. Polom [e, f], A. Kolacinska [g], W. Allum [h], D. D'Ugo [i], H.Z. Malik [j], I.T. Rubio [k], L. Wyld [l], M. Leidenius [m], M. Rivoire [n], O. Zoras [o], W. Polkowski [p], G.J. Poston [q], R.A. Audisio [r], T. Kovacs [s], S. González-Moreno [t], on behalf on the European Society of Surgical Oncology

[a] Institut Bergonié and Université de Bordeaux, Bordeaux, France
[b] Leiden University Medical Center, Leiden, the Netherlands
[c] European Society of Surgical Oncology Clinical Research Committee, Brussels, Belgium
[d] Ghent University Hospital, Ghent, Belgium
[e] University of Siena, Siena, Italy
[f] Medical University of Gdansk, Gdańsk, Poland
[g] Department of Head and Neck Cancer Surgery, Breast Unit, Medical University of Lodz, Cancer Center, Lodz, Poland
[h] Royal Marsden NHS Foundation Trust, London, UK
[i] Fondazione Policlinico Universitario A. Gemelli, Rome, Italy
[j] Aintree University Hospital, Liverpool, UK
[k] Clinica Universidad de Navarra, Madrid, Spain
[l] Medical School, University of Sheffield, Sheffield and Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust, Doncaster, UK
[m] Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland
[n] Centre Léon Bérard and Université de Lyon, Lyon, France
[o] Medical School, University of Crete, Heraklion, Greece
[p] Medical University of Lublin, Poland
[q] University of Liverpool, Liverpool, UK
[r] Institute of Clinical Sciences, Sahlgrenska University Hospital, Göteborg, Sweden
[s] Guy's Hospital, London, UK
[t] MD Anderson Cancer Center, Madrid, Spain

ARTICLE INFO

Article history:
Received 30 November 2018
Received in revised form
26 March 2019
Accepted 4 May 2019
Available online 5 May 2019

Keywords:
Surgical oncology
Oncopolicy
Clinical research
Clinical studies

ABSTRACT

As part of its mission to promote the best surgical care for cancer patients, the European Society of Surgical Oncology (ESSO) has been developing multiple programmes for clinical research along with its educational portfolio. This position paper describes the different research activities of the Society over the past decade and an action plan for the upcoming five years to lead innovative and high quality surgical oncology research. ESSO proposes to consider pragmatic research methodologies as a complement to randomised clinical trials (RCT), advocates for increased funding and operational support in conducting research and aims to enable young surgeons to be active in research and establish partnerships for translational research activities.

Background and rationale of ESSO

In 1981, the European Society of Surgical Oncology (ESSO) was founded to benefit cancer patients through the science and practice of surgical oncology, promoting education, research and leadership in multidisciplinary care. Since then, ESSO has steadily increased its membership and educational portfolio, reaching out to the global surgical community. It has successfully positioned itself as the leading society for surgical oncologists in Europe and as a key player in the oncological arena through its research activities, which increased progressively during the last decade. The

* Corresponding author.
E-mail address: s.evrard@bordeaux.unicancer.fr (S. Evrard).

https://doi.org/10.1016/j.ejso.2019.05.004
0748-7983/

importance of research in oncology is demonstrated by the significant correlation between the number of scientific publications and the proportion of cancer specific mortality per country [1]. In a subset analysis of countries that have less than 1000 publications per year, even a modest increase of a few hundred publications is correlated with a decrease of cancer specific mortality [2].

However, the field of cancer research has become more complex due to advances in technology, (molecular) biology and immune-oncology, making the role of high quality surgical research even more relevant as the world struggles to balance the cost and benefit of treatments.

The key research strategies of ESSO include optimal utilisation of national registries to benchmark surgical practices across Europe, prospective clinical and translational research and partnership with international surgical societies to integrate research in surgical education and training. This ESSO position paper discusses challenges in surgical oncology research and presents a plan of action for the coming five years on how to overcome these hurdles.

Challenges in clinical research in surgical oncology

There is great need for research to demonstrate and establish the impact of surgery in an oncological field that is mainly driven by advances in cancer biology and immune-oncology, yet, only 1% of cancer patients is recruited into surgical oncology trials in Europe. Conducting research in surgical oncology has always been challenging due to a number of surgery-related reasons further detailed below [3].

Variability of complex surgical procedures

The complexity of and variation in disease and accompanying inter-surgeon variability makes it more difficult to produce uniform and standardised outcome measures compared to research focussed on non-surgical treatment. Surgical expertise, learning curve effects, lack of systematic, consistent reports of operative findings and pathological outcomes all contribute to heterogeneous data. This amounts to (statistical) challenges when comparing different surgical treatment strategies.

Trial design for surgical research questions

Defining the research question, endpoint and appropriate trial design are the first steps for developing new clinical trials. Although the gold standard for researching a new treatment is the randomised clinical trial (RCT), this is not always a possibility when investigating surgical treatment options. The randomisation process often lacks equipoise for both surgeons and patients, and patients are generally not willing to accept randomisation to the control arm when a new treatment is available. In 2006, surgical phase III trials represented only 8% of all publications, 1 in 5 surgical studies was prematurely closed and 44% were never published [4]. Less than 50% of surgical trials meet the CONSORT criteria for non-pharmacological trials. Recently, the CONSORT checklist was reduced from 25 items to 10, hoping to improve compliance [5]. Still, the quality of reporting in the surgical literature is poor, and feasible alternative methodologies somewhere on the spectrum between retrospective reports and RCTs are underused, especially in phases II and IV [3]. The role of surgical journals here is crucial. Some of the most highly rated journals are still reluctant to publish well designed prospective phase II studies, even though they are superior to larger retrospective series. This is one of the major reasons why education of surgeons and editors/reviewers of journals is needed to reach high quality research.

Funding

There is a lack of financial and political priority for surgical trials, even though surgery has an enormous impact on cancer patients. Of all public funding towards clinical research in oncology, less than 5% is devoted to surgical research [4]. There is little commercial incentive for companies to fund surgical trials, thus, support is needed from non-profit organisations, corporate social responsibility activities and governments. Alternatively, a stronger collaboration with the medical oncology community could result in more funds, since they do receive substantial support from the pharma industry. This seems a reasonable solution, as the multidisciplinary approach is already the standard in the treatment of patients. For example, a patient suffering from metastasised colorectal cancer can expect improvement not only from new drugs but also from a more advanced surgical strategy, such as the new parenchyma-sparing liver surgery [6]. Both types of treatment need trials to confirm their efficacy.

Furthermore, any research into (neo-)adjuvant systemic therapy cannot be expected to yield scientifically sound results, if equal quality of surgery in both arms cannot be confirmed. There is an urgent need for multidisciplinary leaders of cancer research in Europe to construct a shared vision and a shared commitment to an integrated approach in cancer care. For this, a joint effort in securing funds and support for clinical research is essential.

Impact of advances in (molecular) biology and technology

There has been a seismic shift in the understanding and treatment of cancer, brought on by advances in molecular biology and immune-oncology [7]. Much of the global funding and research efforts have been focused on personalised medicine and new combinations of chemo-, radio- and immunotherapy. Though the role of high quality surgery at all stages of cancer has not diminished, conducting purely surgical trials has become even more difficult. The role of surgeons within research has shifted towards becoming “technicians”, delivering samples for biobanks and translational research. This should be embraced by surgeons and seen as a chance to develop new partnerships with biologists and imaging and technology experts. Young investigators interested in academic careers can become part of innovative research from such fruitful collaborations. An example of this is new research into the impact of local treatments on activating the immune system, which is a real chance for surgeons to become leaders in the current molecular revolution.

ESSO's response to challenges in surgical research

A pan-European infrastructure focussing on the issues described previously is needed to define an agenda for surgical oncology research and to introduce a culture of research among future surgeons. Research methodology has to be adapted in order to achieve this; RCTs should remain the gold standard, but at the same time, a more pragmatic approach should be explored to increase the chances of successfully producing high level evidence for innovative cancer surgery (Fig. 1) [8].

Utilising national cancer registries

The EURECCA project (acronym for European Registration of Cancer Care) was ESSO's first research initiative. This project is a framework to develop a prospective European audit structure, with the goal of improving treatment strategies and making them more accessible to European cancer patients. Through an international network, EURECCA builds a comprehensive approach to capture

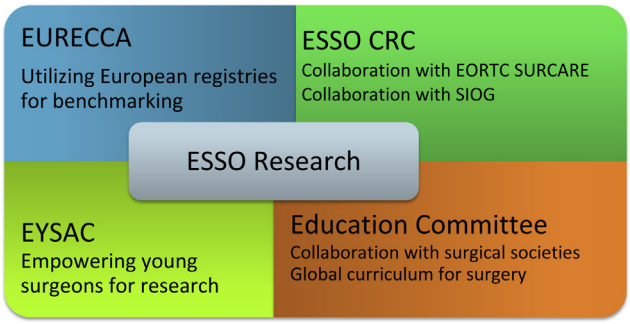

Fig. 1. Committees of ESSO involved in research; ESSO – European Society of Surgical Oncology; EURECCA – European Registry for Cancer Care; ESSO CRC – ESSO Clinical Research Committee; EORTC – European Organization for Research and Treatment of Cancer; SURCARE – High Quality Standards for Prospective Surgical Clinical Research; EYSAC – ESSO Young Surgeons Alumni Club; SIOG – International Society of Geriatric Oncology.

relevant clinical data in various malignancies, which can be used to benchmark surgical quality and clinical practices. Some EURECCA projects are described below to provide an insight in its procedures.

Colorectal cancer

Two international studies using population-based data were conducted to investigate adjuvant treatment variation between European countries. For the first, data was collected from all patients diagnosed with stage II colon cancer between 2004 and 2009 in the Netherlands, Denmark, Sweden, England, Ireland and Belgium (n = 59,154) [9]. The proportion of patients receiving adjuvant chemotherapy ranged from 7% to 29%. No clear pattern was found between the proportion of patients receiving adjuvant chemotherapy and survival. For the second study, data was collected from all patients diagnosed with stage I-III rectal cancer (n = 57,120). The proportion of patients receiving preoperative radiotherapy ranged from 8% to 60% and postoperative chemotherapy ranged from 8% to 39%. These two studies demonstrate that the large differences in treatment strategies did not lead to differences in survival.

Colon cancer in older patients represents a major public health issue. As older patients are seldom included in clinical trials, the optimal treatment for these patients remains unclear. In order to describe treatment variation of patients with colon cancer aged 80 years and older, data from five European cancer registries were obtained (n = 50,761) [10]. Almost all patients underwent surgery but the proportion of adjuvant chemotherapy varied considerably. Despite a higher proportion of patients receiving adjuvant chemotherapy, poorer survival outcomes were observed in Belgium.

Breast cancer

Older patients are also poorly represented in breast cancer research. This EURECCA comparison assessed whether variation in treatment patterns may be associated with variation in survival. The population-based study included patients aged 70 years or older with non-metastatic breast cancer from cancer registries in the Netherlands, Belgium, Ireland, England and Poland (n = 236,015). The proportion of patients with stage I breast cancer receiving endocrine therapy ranged from 20% to 85%, though no differences in survival were observed, suggesting gross overtreatment. On the other hand, the proportion of patients with stage III breast cancer receiving surgery ranged from 50% to 78%, which was accompanied by differences in survival, suggesting potential undertreatment [11].

Pancreatic cancer

Pancreatic cancer is one of the few malignancies with increasing incidence and mortality rates. The aim of this study was to describe variation in adjuvant chemotherapy and survival after primary tumour resection for stage I and II pancreatic cancer (n = 3901). The proportion of patients receiving adjuvant chemotherapy ranged from 41% to 70%. Ninety-day mortality ranged from 1% to 14%, but overall survival (OS) did not differ. This study provides a clear insight into clinical practice in the EURECCA Pancreas consortium, and differences in adjuvant chemotherapy and outcomes provide a basis for further investigation.

Oesophageal and gastric cancer

Two recent comparisons of treatment and outcomes in patients with metastatic gastric cancer and in patients aged 70 years or older were conducted. In the study regarding metastatic gastric cancer (n = 17,493), the proportion of gastric resections varied from 8% to 20%. Administration of chemotherapy ranged from 37% to 62%. Higher proportions of surgery and chemotherapy seem to be associated with better survival.

Prospective international registries and vision for the future

Currently, there are two prospective data collection projects within EURECCA. The International Watch and Wait Database (IWWD) is currently open for inclusion and data are collected regarding rectal cancer patients in whom total mesorectal excision (TME) surgery was delayed or omitted after neoadjuvant therapy [12]. In the International Nipple Sparing Mastectomy Registry (INSPIRE) dataset, recently closed for inclusion, patients with breast cancer who undergo a nipple sparing mastectomy with immediate reconstruction are entered to assess the oncological outcome, complication rate and aesthetic outcomes. Both registries are examples of alternative strategies to RCTs that still provide valid and unbiased scientific insights. Since RCTs are usually not a viable option for researching new surgical treatments, due to lack of funding and unwillingness to randomise, prospective databases provide the solution for developing evidence based treatments. Part of EURECCA's strategy for the future is setting up more prospective registries to gather systematic and valid evidence for new surgical treatments.

Another important aspect of EURECCA's goals are continuing to provide comparisons of treatment strategies between different European countries. By doing so, awareness is created and the large variation is thought-provoking and used to generate new hypotheses for future studies.

Collaboration with EORTC: the SURCARE initiative

In 2015, a Clinical Research Committee (CRC) was set up to partner with the European Organization for Research and Treatment of Cancer (EORTC) in order to systematically develop high quality prospective surgical research. The ESSO CRC is composed of ESSO members that are actively engaged in clinical research, among them several members of the European Young Surgeons Alumni Club (EYSAC).

EORTC and ESSO share a common vision to improve the quality of surgical research in Europe. They also have complementary expertise; ESSO has a huge network of surgeons, scientific guidelines for high quality surgical care and an extensive educational portfolio, while EORTC has expertise in the scientific and operational aspects of international multidisciplinary clinical research. A partnership was established between the two to build SURCARE [13], an infrastructure for quality assurance in prospective clinical research. Through SURCARE, ESSO and EORTC articulate the need for more precision in cancer surgery through prospective, high

quality yet feasible research that focuses on those outcomes that are most relevant for individual patients. Two projects stemmed from this partnership.

CLIMB EORTC 1409/ESSO 01

CLIMB is a prospective colorectal liver metastasis database with an integrated quality assurance programme. Patients are included if they have unresectable, borderline resectable or initially unresectable colorectal liver metastasis, as determined by a multidisciplinary team (MDT) meeting. The primary endpoint is the 30- and 90-day surgical complications, the secondary endpoints are long-term outcomes. Currently, 210 patients are registered, and 126 patients (60%) underwent at least one liver surgery. Most commonly reported complications include wound, urinary tract and intra-abdominal infections, bile leak, post hepatectomy liver failure, anaemia and fluid retention (NCT02218801).

DREAM EORTC 1527/JCOG 1609 INT/ESSO 02

DREAM, diffusion weighted MRI assessment of liver metastasis to improve surgical planning is the first collaborative study between ESSO, EORTC and JCOG, the largest and most influential clinical research group in Japan. Using standard liver imaging and surgery, patients with borderline resectable or unresectable colorectal liver metastases with available CT scan, T1/T2 weighted, Diffusion Weighted (DW) and contrast enhanced (CE) MRI (multiparametric MRIs) will be assessed by an MDT for the appropriate treatment strategy. Treatment naïve patients and those who have started their chemotherapy are both eligible. Both the CT scan and multiparametric MRI at two time points (one before the start of chemotherapy and one before surgery) must be available. All patients who then undergo liver surgery will be followed within DREAM for 2 years. The primary focus of the study will be the analysis of confirmed disappearing liver metastases (cDLM), defined as lesions that disappeared after chemotherapy on both CT scan and multiparametric MRIs. The primary objective is to assess the negative predictive value of preoperative DW-MRI, T1/T2, CE-MRI and standard CT scan combined for identifying non-viable lesions among cDLMs. The true status of the lesions will be assessed by histopathology among those resected and by follow-up imaging among those left in situ. Accrual is on-going (NCT02781935).

Focus on geriatric patients

ESSO has also collaborated with the International Society of Geriatric Oncology (SIOG) surgical task force to create “Go Safe: Geriatric Oncology Surgical Assessment and Functional Recovery after Surgery”. This is an international prospective registry on how frailty, comorbidities, and malnourishment are associated with clinical outcome after surgery in older patients. This registry focuses on patients’ quality of life, as well as functional recovery. This is an important initiative to clarify surgical issues among elderly cancer patients.

Empowering young surgeons

One of the core missions of ESSO is to pave the way for a new generation of surgeons who will not only learn to operate skilfully but also become future key opinion leaders with a deep understanding of cancer biology and clinical research methodology. For this, the European Young Surgeons Alumni Club (EYSAC) has the following research activities.

CORSiCA: complete pathologic response rectal cancers

This is the first EYSAC International, multicentre, retrospective cohort study including rectal cancer patients treated from 2012 to 2017 who underwent TME or local excision with a pathological diagnosis consistent with ypT0, independently from N status. So far, 729 rectal cancer patients have been included in the database from 45 European, Australian, and South American centres. More precise results will be presented after full collection of the data. Preliminary results were presented during the best abstracts session of the 38th ESSO congress in Budapest, Hungary (NCT03351959).

Young for young (Y4Y)

Y4Y is a project of young surgeons for young patients. In the majority of malignancies, the incidence of cancer is strongly linked to age. However, cancer incidence among patients younger than 40 years is also increasing. Very little is known for the majority of these patients, regarding prognosis and over- and undertreatment. These factors, together with quality of life analysis focussed on specific needs of these patients in the 21st century, will be investigated by an international group of young surgeons under the ESSO and EYSAC umbrella.

Vision for the future (5-year plan)

Being involved in clinical research is a major commitment of ESSO and producing high quality and robust evidence is our responsibility. However, challenges remain, and a clear strategy is needed if we are to be successful in our mission. The plan of action for the coming five years consists of 4 pillars (Fig. 2).

1. Money is scarcely available in surgical research. Therefore, surgeons need pragmatic models without compromising quality and science. ESSO aims to collaborate more with oncologists and methodologists and lobby for alternative funding sources, using the impact of cancer surgery on medical oncology and surgical quality in patient outcomes as leverage.
2. As resources are limited, surgeons must carefully select the topic and endpoints of their research, focussing on unmet needs and practice changing questions. Involving young surgeons and multidisciplinary teams to target the right question is key for the future of our research activities. ESSO's CRC and EYSAC provide an environment for young investigators to develop new ideas and optimise design of their studies.
3. In order to develop well-designed and efficient studies, we must enhance our networking. This means sharing our vision and strategy for oncology research and surgical leadership. Strengthening partnerships will be needed with surgical societies like the SSO to harmonize standards of quality and implement a culture of research among surgeons.
4. Surgeons underestimate their role in biological research. Surgery presents a unique opportunity to collect samples from

Fig. 2. ESSO's for pillars of action for improving clinical research in surgery.

primary tumours, peripheral normal tissue and metastases as well as liquid biopsies. We must increase our involvement in defining scientific questions and establishing standards of quality in prospective biobanking processes. Collaborating with biological research teams is an opportunity for excellent translational research linked high quality surgery, molecular biology and the use of technology. Surgeons can be the drivers of such research, like in the translational project of the DREAM study. Fundamental research seems to indicate that local treatments like surgery affect the immune response and could interfere with the progression of cancer [14]. Surgeons have a fantastic opportunity to innovate and lead ground-breaking progress by utilising the techniques they are already familiar with to gain a deeper level of understanding of the biological mechanisms of cancer.

Conclusion

A pan-European infrastructure focussing on the issues described previously is needed to define an agenda for surgical oncology research and to introduce a culture of research among future surgeons. Protocol-driven studies that are well designed with accurate and informative clinical data must be the rule rather than the exception. To achieve this, research methodology has to be adapted; RCTs should remain the gold standard, but at the same time, a more pragmatic approach should be explored to increase the chances of successfully producing high level evidence for innovative cancer surgery. ESSO aims to address these challenges together with its partners, by advocating for surgical research funding, quality assurance, education, global and multidisciplinary collaborations, especially for translational research. ESSO's commitment to high quality surgical research must live up to the complexity of a disease it is willing to fight.

Acknowledgments

ESSO wants to thank the following for their contribution to its programmes of research: the EORTC, Ligue Nationale contre le Cancer, Krebsforschung Schweiz, Anticancer Fund Belgium, the EURECCA initiative.

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